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(54) ANTIGENIC PEPTIDES DERIVED FROM TELOMERASE

VON DER TELOMERASE ABGELEITETE ANTIGENE PEPTIDE

PEPTIDES ANTIGENES DERIVES DE LA TELOMERASE

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(73) Proprietor: **GemVax AS**
0379 Oslo (NO)

(72) Inventors:
- **GAUDERNACK, Gustav**
  N-0310 Oslo (NO)
- **ERIKSEN, Jon, Amund**
  N-3916 Porsgrunn (NO)
- **MOLLER, Mona**
  N-3925 Porsgrunn (NO)
- **GJERTSEN, Marianne Klemp**
  Ullernch. 70, N-0310 Oslo (NO)
- **SAETERDAL, Ingvil**
  N-0310 Oslo (NO)
- **SAEBOE-LARSEN, Stein**
  N-0310 Oslo (NO)

(74) Representative: **Wallace, Sheila Jane et al**
Lloyd Wise
Commonwealth House,
1-19 New Oxford Street
London WC1A 1LW (GB)

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- **ROBERT H. VONDERHEIDE ET AL: 'The Telomerase Catalytic Subunit is a Widely Expressed Tumor-Associated Antigen Recognized by Cytotoxic T Lymphocytes' IMMUNITY vol. 10, 1999, pages 673 - 679, XP000890114**

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Description

[0001] This invention relates to proteins or peptides which elicit T cell mediated immunity, and to cancer vaccines and compositions for anti-cancer treatment comprising such proteins or peptide fragments. This invention also relates to pharmaceutical compositions comprising the proteins or peptides and methods for generating T lymphocytes capable of recognising and destroying tumour cells in a mammal.

[0002] Cancer develops through a multistep process involving several mutational events. These mutations result in altered expression/function of genes belonging to two categories: oncogenes and tumour suppressor genes. Oncogenes arise in nature from proto-oncogenes through point mutations or translocations, thereby resulting in a transformed state of the cell harbouring the mutation. All oncogenes code for and function through a protein. Proto-oncogenes are normal genes of the cell which have the potential of becoming oncogenes, In the majority of cases, proto-oncogenes have been shown to be components of signal transduction pathways. Oncogenes act in a dominant fashion. Tumour-suppressor genes on the other hand, act in a recessive fashion, i.e. through loss of function, and contribute to oncogenesis when both alleles encoding the functional protein have been altered to produce non-functional gene products.

[0003] The concerted action of a combination of altered oncogenes and tumour-suppressor genes results in cellular transformation and development of a malignant phenotype.

[0004] Such cells are however prone to senescence and have a limited life-span. In the majority of cancers, immortalisation of the tumour cells requires the turning on of an enzyme complex called telomerase. In somatic cells the catalytic subunit of this enzyme is normally not expressed. Additional events, such as the action of proteins encoded by a tumour virus or demethylation of silenced promoter sites can result in expression of a functional telomerase complex in tumour cells.

[0005] In the field of human cancer immunology, the last two decades have seen intensive efforts to characterise genuine cancer specific antigens. In particular, effort has been devoted to the analysis of antibodies to human tumour antigens. The prior art suggests that such antibodies can be used for diagnostic and therapeutic purposes, for instance in connection with an anti-cancer agent. However, antibodies can only bind to tumour antigens that are exposed on the surface of tumour cells. For this reason, the efforts to produce a cancer treatment based on the immune system of the body has been less successful than expected.

[0006] A fundamental feature of the immune system is that it can distinguish self from nonself and does not normally react against self molecules. It has been shown that rejection of tissues or organs grafted from other individuals is an immune response to the foreign antigens on the surface of the grafted cells. The immune response in general consists of a humeral response, mediated by antibodies, and a cellular response. Antibodies are produced and secreted by B lymphocytes, and typically recognise free antigen in native conformation. They can therefore potentially recognise almost any site exposed on the antigen surface. In contrast to antibodies, T cells, which mediate the cellular arm of the immune response, recognise antigens only in the context of MHC molecules, and only after appropriate antigen processing. This antigen processing usually consists of proteolytic fragmentation of the protein, resulting in peptides that fit into the groove of the MHC molecules. This enables T cells to also recognise peptides derived from intracellular antigens.

[0007] T cells can recognise aberrant peptides derived from anywhere in the tumour cell, in the context of MHC molecules on the surface of the tumour cell. The T cells can subsequently be activated to eliminate the tumour cell harbouring the aberrant peptide. In experimental models involving murine tumours it has been shown that point mutations in intracellular "self" proteins may give rise to tumour rejection antigens, consisting of peptides differing in a single amino acid from the normal peptide. The T cells recognising these peptides in the context of the major histocompatibility (MHC) molecules on the surface of the tumour cells are capable of killing the tumour cells and thus rejecting the tumour from the host (Boon et al.,1989, Cell 58, 293-303).

[0008] MHC molecules in humans are normally referred to as HLA (human leucocyte associated antigen) molecules. There are two principal classes of HLA molecules, class I and class II. HLA class I molecules are encoded by HLA A, B and C subloci and primarily activate CD8+ cytotoxic T cells. HLA class II molecules, on the other hand, primarily activate CD4+ T cells, and are encoded by the DR, DP and DQ subloci. Every individual normally has six different HLA class I molecules, usually two alleles from each of the three subgroups A, B and C, although in some cases the number of different HLA class I molecules is reduced due to the occurrence of the same HLA allele twice.

[0009] The HLA gene products are highly polymorphic. Different individuals express distinct HLA molecules that differ from those found in other individuals. This explains the difficulty of finding HLA matched organ donors in transplantations. The significance of the genetic variation of the HLA molecules in immunobiology is reflected by their role as immune-response genes. Through their peptide binding capacity, the presence or absence of certain HLA molecules governs the capacity of an individual to respond to specific peptide epitopes. As a consequence, HLA molecules determine resistance or susceptibility to disease.

[0010] T cells may inhibit the development and growth of cancer by a variety of mechanisms. Cytotoxic T cells, both

HLA class I restricted CD8+ and HLA class II restricted CD4+ may directly kill tumour cells presenting the appropriate tumour antigens. Normally, CD4+ helper T cells are needed for cytotoxic CD8+ T cell responses, but if the peptide antigen is presented by an appropriate APC, cytotoxic CD8+ T cells can be activated directly, which results in a quicker, stronger and more efficient response.

[0011] While the peptides that are presented by HLA class II molecules are of varying length (12-25 amino acids), the peptides presented by HLA class I molecules must normally be exactly nine amino acid residues long in order to fit into the class I HLA binding groove. A longer peptide will result in non-binding if it cannot be processed internally by an APC or target cell, such as a cancer cell, before presenting in the class I HLA groove. Only a limited number of deviations from this requirement of nine amino acids have been reported, and in those cases the length of the presented peptide has been either eight or ten amino acid residues long.

[0012] Reviews of how MHC binds peptides can be found in Hans-Georg Rammensee, Thomas Friede and Stefan Stevanovic, (1995, Immunogenetics, 41, 178-228) and in Barinaga (1992, *Science* 257, 880-881). Male et al (1987, Advanced *Immunology,* J.B. Lippincott Company, Philadelphia) offers a more comprehensive explanation of the technical background to this invention.

[0013] In our International Application WO92/14756, we described synthetic peptides and fragments of oncogene protein products which have a point of mutation or translocations as compared to their proto-oncogene or tumour suppressor gene protein. These peptides correspond to, completely cover or are fragments of the processed oncogene protein fragment or tumour suppressor gene fragment as presented by cancer cells or other antigen presenting cells, and are presented as a HLA-peptide complex by at least one allele in every individual. These peptides were also shown to induce specific T cell responses to the actual oncogene protein fragment produced by the cell by processing and presented in the HLA molecule. In particular, we described peptides derived from the p21-*ras* protein which had point mutations at particular amino acid positions, namely positions 12, 13 and 61. These peptides have been shown to be effective in regulating the growth of cancer cells *in vitro*. Furthermore, the peptides were shown to elicit CD4+ T cell immunity against cancer cells harbouring the mutated p21-*ras* oncogene protein through the administration of such peptides in vaccination or cancer therapy schemes. Later we have shown that these peptides also elicit CD8+ T cell immunity against cancer cells harbouring the mutated p21 *ras* oncogene protein through the administration mentioned above (see M.K. Gjertsen et al., Int. J cancer, 1997, vol. 72 p. 784).

[0014] However, the peptides described above will be useful only in certain numbers of cancers, namely those which involve oncogenes with point mutations or translocation in a proto-oncogene or tumour suppressor gene. There is therefore a strong need for an anticancer treatment or vaccine which will be effective against a more general range of cancers.

[0015] In general, tumours are very heterogeneous with respect to genetic alterations found in the tumour cells. This implies that both the potential therapeutic effect and prophylactic strength of a cancer vaccine will increase with the number of targets that the vaccine is able to elicit T cell immunity against. A multiple target vaccine will also reduce the risk of new tumour formation by treatment escape variants from the primary tumour.

[0016] The enzyme telomerase has recently been the focus of attention for its supposed role in prevention of cellular ageing. Telomerase is a RNA-dependent DNA polymerase, which synthesises telomeric DNA repeats using an RNA template that exists as a subunit of the telomerase holoenzyme. The DNA repeats synthesised by the enzyme are incorporated into telomeres, which are specialised DNA-protein structures found at the ends of the linear DNA molecules which make up every chromosome. Telomerase was first identified in the ciliate *Tetrahymena* (Greider and Blackburn, 1985, *Cell* 43, 405-413). A human telomerase catalytic subunit sequence was recently identified by Meyerson et al (1990, *Cell* 1197 , 785-795), and Nakamura et al (1997, *Science* 277, 955-959), who respectively named the gene hEST2 and hTRT. In addition, three other proteins which are associated with telomerase activity have also been identified: p80 and p95 of *Tetrahymena* (Collins et al, 1995, *Cell* 81, 677-686) and TP1/TLP1, which is the mammalian homologue of *Tetrahymena* p80 (Harrington et al, 1997, *Science,* 275, 973-977; Nakayama et al., 1997, *Cell* 88, 875-884).

[0017] Telomerase is not expressed in most normal cells in the body. Most somatic lineages in humans show no detectable telomerase activity, but telomerase activity is detected the germline and in some stem cell compartments, which are sites of active cell division (Harley et al., 1994, *Cold Spring Harbor Symp. Quant. Biol.* 59, 307-315; Kim et al., 1994, *Science* 266, 2011-2015; Broccoli et al, 1995, *PNAS USA* 92, 9082-9086; Counter et al., 1995, *Blood* 85, 2315-2320; Hiyama et al., 1995, *J. Immunol.* 155, 3711-3715). Telomeres of most types of human somatic cells shorten with increasing age of the organism, consistent with lack of telomerase activity in these cells. Cultured human cells also show telomere shortening. Telomere shortening continues in cultured human cells which have been transformed, until the telomeres have become critically short. At this point, termed the crisis point, significant levels of cell death and karyotypic instability are observed.

[0018] Immortal cells, which have acquired the ability to grow indefinitely in culture, emerge at rare frequency from crisis populations. These immortal cells have high levels of telomerase activity and stable telomeres. Telomerase activity is also readily detected in the great majority of human tumour samples analysed to date (Kim et al, 1994, *Science*

266, 2011-2015), including ovarian carcinoma (Counter et al., 1994, *PNAS USA* 91, 2900-2904). A comprehensive review is provided by Shay and Bachetti (1997, *Eur. J. Cancer* 33, 787-791). Thus, activation of telomerase may overcome the barriers to continuous cell division imposed by telomere length. Cells that overcome the normal senescence mechanisms may do so by stabilising telomere length, probably due to the activity of telomerase.

[0019] Viruses implicated in human cancer development such as Epstein Barr virus (EBV, related to B cell malignancies and nasopharyngeal carcinomas) and Human Papilloma virus (HPV 16 and 18, related to cervical carcinomas) have long been known to have the capacity to immortalize human cells. It has now been demonstrated that induction of telomerase activity is the key element in this process (Klingelhutz et al, 1996, *Nature,* 380, 79-82).

[0020] Telomerase is therefore a potential target for cancer therapy. Thus, telomerase inhibitors have been proposed as a new class of anti-cancer drugs (reviewed in Sharma et al, 1997, *Ann Oncol* 8(11), 1063-1074; Axelrod, 1996, *Nature Med* 2(2), 158-159; Huminiecki, 1996, *Acta Biochim Pol*, 43(3), 531-538). It has been suggested that the identification of a human telomerase catalytic subunit may provide a biochemical reagent for identifying such drugs (Meyerson et al, 1990, *Cell* 1197, 785-795). Telomerase has also been suggested to be a marker for diagnosis or prognosis of cancer (Soria and Rixe, 1997, *Bull Cancer* 84(10), 963-970; Dahse et al, 1997, *Clin Chem* 43(5), 708-714).

[0021] As far as we are aware, however, no one has previously suggested that telomerase may function as a useful target for T cell mediated therapy, or that telomerase peptides or proteins may be used for the treatment or prophylaxis of cancer.

[0022] According to one aspect of the present invention, there is provided the use of a peptide for the manufacture of a medicament for the treatment or prophylaxis of cancer, the peptide comprising a sequence EARPALLTSRLRFIPK (SEQ ID NO: 2), DGLRPIVNMDYVVGAR (SEQ ID NO: 3), GVPEYGCVVNLRKTVVNF (SEQ ID NO: 4), ILAKFLHWL (SEQ ID NO: 9) or ELLRSFFYV (SEQ ID NO: 10), the treatment or prophylaxis comprising generating a T cell response, the response being against the peptide EARPALLTSRLRFIPK (SEQ ID NO: 2), DGLRPIVNMDYVVGAR (SEQ ID NO: 3), GVPEYGCVVNLRKTVVNF (SEQ ID NO: 4), ILAKFLHWL (SEQ ID NO: 9) or ELLRSFFYV (SEQ ID NO: 10) or a fragment thereof, at least 8 amino acids long, producible after processing by an antigen presenting cell.

[0023] According to another aspect of the present invention, there is provided the use of a nucleic acid for the manufacture of a medicament for the treatment or prophylaxis of cancer, in which the nucleic acid is capable of encoding a peptide comprising a sequence EARPALLTSRLRFIPK (SEQ ID NO: 2), DGLRPIVNMDYVVGAR (SEQ ID NO: 3), GVPEYGCVVNLRKTVVNF (SEQ ID NO: 4), ILAKFLHWL (SEQ ID NO: 9) or ELLRSFFYV (SEQ ID NO: 10), the treatment or prophylaxis comprising generating a T cell response, the response being against the peptide EARPALLTSRLRFIPK (SEQ ID NO: 2), DGLRPIVNMDYWGAR (SEQ ID NO: 3), GVPEYGCVVNLRKTVVNF (SEQ ID NO: 4), ILAKFLHWL (SEQ ID NO: 9) or ELLRSFFYV (SEQ ID NO: 10) or a fragment thereof, at least 8 amino acids long, producible after processing by an antigen presenting cell.

[0024] According to a further aspect to the present invention, there is provided a method of generating T lymphocytes capable of recognising and destroying tumour cells in a mammal, in which the method comprises culturing a sample of T lymphocytes taken from a mammal in the presence of a peptide in an amount sufficient to generate telomerase specific T lymphocytes, in which the peptide comprises a sequence EARPALLTSRLRFIPK (SEQ ID NO: 2), DGLRPIVNMDYVVGAR (SEQ ID NO: 3), GVPEYGCVVNLRKTVVNF (SEQ ID NO: 4), ILAKFLHWL (SEQ ID NO: 9) or ELLRSFFYV (SEQ ID NO: 10). wherein the telomerase specific T lymphocytes generate a response against the peptide EARPALLTSRLRFIPK (SEQ ID NO: 2), DGLRPIVNMDYVVGAR (SEQ ID NO: 3), GVPEYGCVVNLRKTVVNF (SEQ ID NO: 4), ILAKFLHWL (SEQ ID NO: 9) or ELLRSFFYV (SEQ ID NO: 10) or a fragment thereof, at least 8 amino acids long, producible after processing by an antigen presenting cell.

[0025] According to a further aspect of the present invention, there is provided the use of a combination of a telomerase peptide and a peptide capable of inducing a T cell response against an oncogene or mutant tumour suppressor protein or peptide for the manufacture of a medicament for the treatment or prophylaxis of cancer, wherein the telomerase peptide comprises a sequence EARPALLTSRLRFIPK (SEQ ID NO: 2), DGLRPIVNMDYWGAR (SEQ ID NO: 3), GVPEYGCVVNLRKTVVNF (SEQ ID NO: 4), ILAKFLHWL (SEQ ID NO: 9) or ELLRSFFYV (SEQ ID NO: 10), and the treatment or prophylaxis comprises generating a T cell response, the response being against the peptide EARPALLTSRLRFIPK (SEQ ID NO: 2), DGLRPIVNMDYVVGAR (SEQ ID NO: 3), GVPEYGCVVNLRKTVVNF (SEQ ID NO: 4), IIAKFLHWL (SEQ ID NO: 9) or ELLRSFFYV (SEQ ID NO: 10) or a fragment thereof, at least 8 amino acids long, producible after processing by an antigen presenting cell.

[0026] There is disclosed herein a telomerase protein or peptide for use in the treatment or prophylaxis of cancer.

[0027] There is also disclosed a nucleic acid for use in the treatment or prophylaxis of cancer, the nucleic acid being capable of encoding a telomerase protein or peptide as described above.

[0028] There is also disclosed a pharmaceutical composition comprising at least one telomerase protein or peptide or nucleic acid as described above and a pharmaceutically acceptable carrier or diluent.

[0029] Also disclosed herein is the preparation of a pharmaceutical composition as described above, the method comprising mixing at least one telomerase protein or peptide or nucleic acid as previously described with a pharmaceutically acceptable carrier or diluent.

[0030] There is also disclosed a pharmaceutical composition comprising a combination of at least one telomerase protein or peptide as described above and at least one peptide capable of inducing a T cell response against an oncogene or mutant tumour suppressor protein or peptide, together with a pharmaceutically acceptable carrier or diluent.

[0031] Also disclosed herein is a method for the preparation of a pharmaceutical composition as described above, the method comprising mixing at least one telomerase protein or peptide described above, with at least one peptide capable of inducing a T cell response against an oncogene or tumour suppressor protein or peptide, and a pharmaceutically acceptable carrier or diluent.

[0032] Also disclosed herein is the use, in the preparation of a medicament for the treatment or prophylaxis of cancer, of a telomerase protein or peptide, or a nucleic acid capable of encoding a telomerase protein or peptide.

[0033] There is also disclosed a method of generating T lymphocytes capable of recognising and destroying tumour cells in a mammal, comprising taking a sample of T lymphocytes from a mammal, and culturing the T lymphocyte sample in the presence of telomerase protein or peptide in an amount sufficient to generate telomerase protein or peptide specific T lymphocytes.

[0034] The invention is more particularly described, by way of example only, below.

[0035] In this specification, the designations A2, A1, A3 and B7 indicate peptides which are likely to be presented by HLA-A2, HLA-A1, HLA-A3 and HLA-B7 respectively.

[0036] We provide a telomerase protein or peptide for use in a method of treatment or prophylaxis of cancer comprising SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 9 or SEQ ID NO: 10. The peptide generates a T cell response against telomerase, the response being against the peptide EARPALLTSRLRFIPK (SEQ ID NO: 2), DGLRPIVNMDYVVGAR (SEQ ID NO: 3), GVPEYGCVVNLRKTVVNF (SEQ ID NO: 4), ILAKFLHWL (SEQ ID NO: 9) or ELLRSFFYV (SEQ ID NO: 10) or a fragment thereof, at least 8 amino acids long, producible after processing by an antigen presenting cell. The peptide may be for use in a method comprising administering to a mammal, preferably a human, suffering or likely to suffer from cancer a therapeutically effective amount of the telomerase protein or peptide so that a T cell response against the telomerase is induced in the mammal.

[0037] Telomerase specific T cells may be used to target cells which express telomerase. Thus, since most cells in the body of an organism do not express telomerase, they will be unaffected. However, tumour cells that express telomerase will be targeted and destroyed. As telomerase activity has been detected in the majority of cancers identified so far, we expect our materials and methods to have widespread utility.

[0038] Cancers which are suitable for treatment include, but are not limited to, breast cancer, prostate cancer, pancreatic cancer, colo-rectal cancer, lung cancer, malignant melanoma, leukaemias, lymphomas, ovarian cancer, cervical cancer and biliary tract carcinomas.

[0039] As used here, the term telomerase denotes a ribonucleoprotein enzyme which has telomere elongating activity. Telomerase protein as used here denotes any protein component of telomerase, including any subunit having catalytic activity.

[0040] Preferably the telomerase protein is a mammalian telomerase protein, and most preferably a human telomerase protein. The human telomerase protein is preferably the telomerase catalytic subunit identified as hTRT by Nakamura et al (1997, *Science* 277, 955-959) and hEST2 by Meyerson et al (1990, *Cell* 1197, 785-795), the cDNA sequences of which are deposited as GenBank accession numbers AF015950 and AF018167 respectively.

[0041] The term telomerase peptide as used here means a peptide which has an amino acid sequence corresponding to a sequence present in the amino acid sequence of a telomerase protein. The telomerase peptides preferably contain between 9 and 25 amino adds. For instance, the telomerase peptides contain 9, 12, 13, 16 or 21 amino acids.

[0042] The telomerase protein or peptide is chosen so that it generates a T cell response directed against the telomerase protein (or against the telomerase protein from which the telomerase peptide is derived). In particular, the T cell response is generated such that there is a response elicited to the peptide EARPALLTSRLRFIPK (SEQ ID NO: 2), DGLRPIVNMDYVVGAR (SEQ ID NO: 3), GVPEYGCVVNLRKTVVNF (SEQ ID NO: 4), ILAKFLHWL (SEQ ID NO: 9) or ELLRSFFYV (SEQ ID NO: 10) or a fragment thereof, at least 8 amino acids long, producible after processing by an antigen presenting cell. In preferred embodiments, the T cell response induced is a cytotoxic T cell response. The cytotoxic T cell response may be a CD4+ T cell response, or it may be a CD8+ T cell response. In any case, the peptide must be capable of being presented as a complex with a MHC class I or class II protein on the surface of tumour cells or antigen presenting cells, with antigen processing taking place beforehand if necessary.

[0043] The telomerase peptide comprises the sequence of SEQ ID NO : 2, 3, 4, 9 or 10. In addition to this sequence, the peptide may include one or more amino acid residues from an amino acid motif essential for the biological function of the telomerase protein; in other words, it may overlap at least partially with such an amino acid motif. Examples of such amino acid motifs are motifs 1 to 6 of the human telomerase catalytic subunit sequence hEST2 as identified by Meyerson et al (1990, *Cell* 1197, 785-795), in other words, from the motifs

LLRSFFYVTE

SRLRFIPK,
LRPIVNMDYVVG,
PELYFVKVDVTGAYDTI,
KSYVQCQGIPQGSILSTLLCSLCY,
LLLRLVDDFLLVT and
GCVVNLRKTVV

or from any of motifs T, 1, 2, A, B', C, D or E as identified by Nakamura et al (1997, *Science* 277, 955-959) in the hTRT sequence, namely, the motifs

WLMSVYVVELLRSFFYVTETTFQKNRLFFYRKSVWSKLQSIGIRQHLK,
EVRQHREARPALLTSRLRFIPKPDG,
LRPIVNMDYVVGARTFRREKRAERLTSRV,
PPPELYFVKVDVTGAYDTIPQDRLTEVIASIIKP,
KSYVQCQGIPQGSILSTLLCSLCYGDMENKLFAGI,
LLRLVDDFLLVTPHLTH,
AKTFLRTLVRGVPEYGCVVNLRKTVV and HGLFPWCGLLL.

[0044] Suitable peptides which may be used in the methods and compositions described here comprises the sequence of SEQ ID NO: 2, 3, 4, 9 or 10. In addition, they may also comprise other sequences set out in TABLE 1 as well as in the attached sequence identity list.

[0045] Another set of suitable peptides derived from elsewhere in the telomerase sequence, which the peptides of the invention may comprise in addition to SEQ ID NO : 2, 3, 4, 9 or 10, are set out in TABLE 2.

[0046] Also included are proteins and peptides having, in addition to the sequence of SEQ ID NO : 2,3,4,9, or 10, amino acid sequences corresponding to an amino acid sequence present in the amino acid sequence of mammalian homologues of the *Tetrahymena* telomerase associated proteins p80 and p95. For example, the p80 homologues TP1 and TLP1 (Harrington et al, 1997, *Science,* 275, 973-977; Nakayama et al., 1997, *Cell* 88, 875-884).

[0047] Larger peptide fragments carrying a few amino acid substitutions at either the N-terminal end or the C-terminal end, in addition to the sequence of SEQ ID NO: 2, 3, 4, 9, or 10, are also included, as it has been established that such peptides may give rise to T cell clones having the appropriate specificity.

[0048] The peptides described here are particularly suited for use in a vaccine capable of safely eliciting either CD4+ or CD8+ T cell immunity:

a) the peptides are synthetically produced and therefore do not include transforming cancer genes or other sites or materials which might produce deleterious effects,
(b) the peptides may be used alone to induce cellular immunity,
(c) the peptides may be targeted for a particular type of T cell response without the side effects of other unwanted responses.

[0049] The telomerase peptides or proteins described here can be administered in an amount in the range of 1 microgram (1μg) to 1 gram (1g) to an average human patient or individual to be vaccinated. It is preferred to use a smaller dose in the range of 1 microgram (1μg) to 1 milligram (1mg) for each administration.

[0050] In preferred embodiments, the telomerase protein or peptide is provided to the patient in the form of a pharmaceutical composition. The telomerase protein or peptide may be administered as a mixture of proteins or a mixture of proteins and peptides or a mixture of peptides. The pharmaceutical composition may in addition include the usual additives, diluents, stabilisers or the like as known in the art.

[0051] The pharmaceutical composition may comprise one or more telomerase proteins or peptides. The protein or peptide mixture may be any one of the following:

(a) a mixture of peptides having different sequences, for example, corresponding to different portions of a telomerase protein sequence;
(b) a mixture of peptides having overlapping sequences, but suitable to fit different HLA alleles;
(c) a mixture of both mixtures (a) and (b);
(d) a mixture of several mixtures (a);
(e) a mixture of several mixtures (b);
(f) a mixture of several mixtures (a) and several mixtures (b);

[0052] In each case, a mixture of proteins or peptides corresponding to different telomerase proteins, for example,

a telomerase catalytic subunit and a *Tetrahymena* p80 or p95 homologue, may also be used.

[0053] Alternatively, the telomerase peptides in the mixture may be covalently linked with each other to form larger polypeptides or even cyclic polypeptides. The pharmaceutical composition may be made by mixing the telomerase protein(s) or peptide(s) with a pharmaceutically acceptable carrier or diluent.

[0054] The pharmaceutical composition may also include at least one peptide capable of inducing a T cell response against an oncogene or mutant tumour suppressor protein or peptide. Alternatively, the telomerase proteins or peptides may be administered either simultaneously or in optional sequence with these peptides. Examples of oncogene proteins are the p21-ras proteins H-ras, K-ras and N-ras, abl, gip, gsp, ret and trk. Preferably, the oncogene protein or peptide is a p21-ras protein or peptide, for example, the p21-ras peptides described in our International Application WO92/14756. Tumour suppressor proteins include p53 and Rb (retinoblastoma). Such a pharmaceutical composition may be made by mixing the telomerase protein(s) or peptide(s) with the mutant tumour suppressor or oncogene proteins or peptides, together with a pharmaceutically acceptable carrier or diluent.

[0055] As used here, the term mutant refers to a wild type sequence which has one or more of the following: point mutation (transition or transversion), deletion, insertion, duplication translocation or inversion. The term pharmaceutical composition not only encompasses a composition usable in treatment of cancer patients, but also includes compositions useful in connection with prophylaxis, i.e., vaccine compositions.

[0056] The telomerase peptides or proteins are administered to a human individual in need of such treatment or prophylaxis. The administration may take place one or several times as suitable to establish and/or maintain the wanted T cell immunity. The peptides may be administered together, either simultaneously or separately, with compounds such as cytokines and/or growth factors, i.e., interleukin-2 (IL-2), interleukin-12 (IL-12), granulocyte macrophage colony stimulating factor (GM-CSF) or the like in order to strengthen the immune response as known in the art. The telomerase proteins or peptides can be used in a vaccine or a therapeutical composition either alone or in combination with other materials. For example, the peptide or peptides may be supplied in the form of a lipopeptide conjugate which is known to induce a high-affinity cytotoxic T cell response (Deres, 1989, *Nature* 342).

[0057] The peptides and proteins mentioned above as possible constituents of the pharmaceutical composition may be provided in the form of nucleic acid encoding the particular peptide or protein. Thus, the pharmaceutical composition may consist of peptide and/or protein alone, or in combination with nucleic acid, or it may consist of mixtures of nucleic acids.

[0058] The telomerase peptides or proteins may be administered to an individual in the form of DNA vaccines. The DNA encoding the telomerase peptide or protein may be in the form of cloned plasmid DNA or synthetic oligonucleotide. The DNA may be delivered together with cytokines, such as IL-2, and/or other co-stimulatory molecules. The cytokines and/or co-stimulatory molecules may themselves be delivered in the form of plasmid or oligonucleotide DNA.

[0059] The response to a DNA vaccine has been shown to be increased by the presence of immunostimulatory DNA sequences (ISS). These can take the form of hexameric motifs containing methylated CpG, according to the formula : 5'-purine-purine-CG-pyrimidine-pyrimidine-3'. Our DNA vaccines may therefore incorporate these or other ISS, in the DNA encoding the telomerase peptide or protein, in the DNA encoding the cytokine or other co-stimulatory molecules, or in both. A review of the advantages of DNA vaccination is provided by Tighe et al (1998, *Immunology Today,* 19(2), 89-97).

[0060] We describe a protein or polypeptide for use in the treatment of a patient afflicted with cancer, the use comprising eliciting T-cell responses through stimulating *in vivo* or *ex vivo* with the telomerase protein or peptide. The telomerase protein or peptide can also be used in a method of vaccination of a patient in order to obtain resistance against cancer. A suitable method of vaccination comprises eliciting T-cell responses through stimulating *in vivo* or *ex vivo* with a telomerase protein or peptide. We also describe a protein or polypeptide for use in a method of treatment or prophylaxis of cancer, comprising administering to a mammal suffering or likely to suffer from cancer a therapeutically effective amount of the telomerase protein or peptide so that a T cell response against telomerase is induced in the mammal. In particular, the T cell response is against the peptide EARPALLTSRLRFIPK (SEQ ID NO: 2), DGLRPIVNMDYVVGAR (SEQ ID NO: 3), GVPEYGCVVNLRKTVVNF (SEQ ID NO: 4), ILAKFLHWL (SEQ ID NO: 9) or ELLRSFFYV (SEQ ID NO: 10) or a fragment thereof, at least 8 amino acids long, producible after processing by an antigen presenting cell.

[0061] The peptides described here may be produced by conventional processes, for example, by the various peptide synthesis methods known in the art. Alternatively, they may be fragments of a telomerase protein produced by cleavage, for example, using cyanogen bromide, and subsequent purification. Enzymatic cleavage may also be used. The telomerase proteins or peptides may also be in the form of recombinant expressed proteins or peptides.

[0062] Nucleic acids encoding the telomerase peptide can be made by oligonucleotide synthesis. This may be done by any of the various methods available in the art. A nucleic acid encoding telomerase protein may be cloned from a genomic or cDNA library, using conventional library screening. The probe may correspond to a portion of any sequence of a known telomerase gene. Alternatively, the nucleic acid can be obtained by using the Polymerase Chain Reaction (PCR). The nucleic acid is preferably DNA, and may suitably be cloned into a vector. Subclones may be generated by

using suitable restriction enzymes. The cloned or subcloned DNA may be propagated in a suitable host, for example a bacterial host. Alternatively, the host can be a eukaryotic organism, such as yeast or baculovirus. The telomerase protein or peptides may be produced by expression in a suitable host In this case, the DNA is cloned into an expression vector. A variety of commercial expression kits are available. The methods described in Maniatis et al (1991, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor, New York, Cold Spring Harbor Laboratory Press) and Harlow and Lane (1988,
Antibodies: A Laboratory Manual, Cold Spring Harbor, New York, Cold Spring Harbor Laboratory Press) may be used for these purposes.

Experimental Methods

[0063] The peptides were synthesised by using continuous flow solid phase peptide synthesis. N-a-Fmoc-amino acids with appropriate side chain protection were used. The Fmoc-amino acids were activated for coupling as pentafluorophenyl esters or by using either TBTU or diisopropyl carbodiimide activation prior to coupling. 20% piperidine in DMF was used for selective removal of Fmoc after each coupling. Cleavage from the resin and final removal of side chain protection was performed by 95% TFA containing appropriate scavengers. The peptides were purified and analysed by reversed phase (C18) HPLC. The identity of the peptides was confirmed by using electro-spray mass spectroscopy (Finnigan mat SSQ710).

[0064] In order for a cancer vaccine and methods for specific cancer therapy based on T cell immunity to be effective, three conditions must be met:

(a) the peptide is at least 8 amino acids long and is a fragment of a telomerase protein and
(b) the peptide is capable of inducing, either in its full length or after processing by antigen presenting cell, T cell responses.

[0065] The following experimental methods may be used to determine if these three conditions are met for a particular peptide. First, it should be determined if the particular peptide gives rise to T cell immune responses *in vitro.* It will also need to be established if the synthetic peptides correspond to, or are capable after processing to yield, peptide fragments corresponding to peptide fragments occurring in cancer cells harbouring telomerase or antigen presenting cells that have processed naturally occurring telomerase. The specificity of T cells induced *in vivo* by telomerase peptide vaccination may also be determined.

[0066] It is necessary to determine if telomerase expressing tumour cell lines can be killed by T cell clones obtained from peripheral blood from carcinoma patients after telomerase peptide vaccination. T cell clones are obtained after cloning of T-cell blasts present in peripheral blood mononuclear cells (PBMC) from a carcinoma patient after telomerase peptide vaccination. The peptide vaccination protocol includes several *in vivo* injections of peptides intracutaneously with GM-CSF or another commonly used adjuvant. Cloning of T cells is performed by plating responding T cell blasts at 5 blasts per well onto Terasaki plates. Each well contains 2 x 10^4 autologous, irradiated (30 Gy) PBMC as feeder cells. The cells are propagated with the candidate telomerase peptide at 25 mM and 5 U/ml recombinant interleukin-2 (rIL-2) (Amersham, Aylesbury, UK) in a total volume of 20 mL. After 9 days T cell clones are transferred onto flat-bottomed 96-well plates (Costar, Cambridge, MA) with 1 mg/ml phytohemagglutinin (PHA, Wellcome, Dartford, UK), 5 U/ml rIL-2 and allogenic irradiated (30 Gy) PBMC (2 x 10^5) per well as feeder cells. Growing clones are further expanded in 24-well plates with PHA / rIL-2 and 1 x 10^6 allogenic, irradiated PBMC as feeder cells and screened for peptide specificity after 4 to 7 days.

[0067] T cell clones are selected for further characterisation. The cell-surface phenotype of the T cell clone is determined to ascertain if the T cell clone is CD4+ or CD8+. T cell clone is incubated with autologous tumour cell targets at different effector to target ratios to determine if lysis of tumour cells occurs. Lysis indicates that the T cell has reactivity directed against a tumour derived antigen, for example, telomerase protein.

[0068] In order to verify that the antigen recognised is associated with telomerase protein, and to identify the HLA class I or class II molecule presenting the putative telomerase peptide to the T cell clone, different telomerase expressing tumour cell lines carrying one or more HLA class I or II molecules in common with those of the patient are used as target cells in cytotoxicity assays. Target cells are labelled with ^{51}Cr or ^{3}H-thymidine (9.25 x 10^4 Bq/mL) overnight, washed once and plated at 5000 cells per well in 96 well plates. T cells are added at different effector to target ratios and the plates are incubated for 4 hours at 37°C and then harvested before counting in a liquid scintillation counter (Packard Topcount). For example, the bladder carcinoma cell line T24 (12Val$^+$, HLA-A1$^+$, B35$^+$), the melanoma cell line FMEX (12Val$^+$, HLA-A2$^+$, B35$^+$) and the colon carcinoma cell line SW 480 (12Val$^+$, HLA-A2$^+$, B8$^+$) or any other telomerase positive tumour cell line may be used as target cells. A suitable cell line which does not express telomerase protein may be used as a control, and should not be lysed. Lysis of a particular cell line indicates that the T cell clone being tested recognises an endogenously-processed telomerase epitope in the context of the HLA class I or class II

subtype expressed by that cell line.

[0069] The HLA class I or class II restriction of a T cell clone may be determined by blocking experiments. Monoclonal antibodies against HLA class I antigens, for example the panreactive HLA class I monoclonal antibody W6/32, or against class II antigens, for example, monoclonals directed against HLA class II DR, DQ and DP antigens (B8/11, SPV-L3 and B7/21), may be used. The T cell clone activity against the autologous tumour cell line is evaluated using monoclonal antibodies directed against HLA class I and class II molecules at a final concentration of 10 mg/ml. Assays are set up as described above in triplicate in 96 well plates and the target cells are preincubated for 30 minutes at 37°C before addition of T cells.

[0070] The fine specificity of a T cell clone may be determined using peptide pulsing experiments. To identify the telomerase peptide actually being recognised by a T cell clone, a panel of nonamer peptides is tested. ^{51}Cr or ^{3}H-thymidine labelled, mild acid eluted autologous fibroblasts are plated at 2500 cells per well in 96 well plates and pulsed with the peptides at a concentration of 1 mM together with b2-microglobulin (2.5 mg/mL) in a 5% CO_2 incubator at 37°C before addition of the T cells. Assays are set up in triplicate in 96 well plates and incubated for 4 hours with an effector to target ratio of 5 to 1. Controls can include T cell clone cultured alone, with APC in the absence of peptides or with an irrelevant melanoma associated peptide MART-1/Melan-A peptide.

[0071] An alternative protocol to determine the fine specificity of a T cell clone may also be used. In this alternative protocol, the TAP deficient T2 cell line is used as antigen presenting cells. This cell line expresses only small amounts of HLA-A2 antigen, but increased levels of HLA class I antigens at the cell surface can be induced by addition of b2-microglobulin. ^{3}H-labelled target cells are incubated with the different test peptides and control peptides at a concentration of 1 mM together with b2-microglobulin (2.5 mg/mL) for one hour at 37°C. After peptide pulsing, the target cells are washed extensively, counted and plated at 2500 cells per well in 96 well plates before addition of the T cells. The plates are incubated for 4 hours at 37°C in 5% CO_2 before harvesting. Controls include T cell clone cultured alone or with target cells in the absence of peptides. Assays were set up in triplicate in 96 well plates with an effector to target ratio of 20 to 1.

[0072] The sensitivity of a T cell clone to a particular peptide identified above may also be determined using a dose-response experiment. Peptide sensitised fibroblasts can be used as target cells. The target cells are pulsed with the particular peptide as described above for fine specificity determination, with the exception that the peptides are added at different concentrations before the addition of T cells. Controls include target cells alone and target cells pulsed with the irrelevant melanoma associated peptide Melan-A/Mart-1.

Biological experiments / Description of the figures:

Figure 1

[0073] Figure 1 (Fig. 1) describes the induction of telomerase (hTERT) reactive cytotoxic T lymphocytes (CTL's) in HLA-A2 ($A2/K^b$) transgenic mice immunized with telomerase peptides with sequence identity 9 and 10. A standard HLA-A2 restricted influenza (58-66) peptide was used as control. Three groups of five mice each were given two weekly subcutaneous injections of 10^7 irradiated, peptide pulsed (100 μg/ml) syngeneic spleen cells. One week after the second injection, the mice were sacrificed and their spleens harvested. Spleen cells were prepared by standard techniques, and cells from primed animals were restimulated in vitro for 5 days by coculture with peptide pulsed (10 μg/ml) irradiated auatologous spleen cells as antigen presenting cells before testing of cytotoxicity against hTERT expressing target cells (Jurkat) transfected with HLA-A2 ($A2/K^b$) in a ^{51}Cr release assay.

[0074] Columns to the left of Fig. 1 show killing of HLA-A2 transfected Jurkat cells pulsed with the control peptide (influenza 58-66) by T cells obtained after priming of mice with the peptide with sequence identity 9, at different effector to target ratios. Specific cytotoxicity above background was observed at all effector to target ratios. Columns in the middle show similar data with T cells obtained from mice primed with the peptide with sequence identity 10. Significant killing of Jurkat cells was only observed when spleen cells from telomerase peptide pulsed mice were used as effector cells, thus when spleen cells from influenza peptide primed mice were used as effectors, only background level of killing of Jurkat cells was seen when the target cells were pulsed with an irrelevant peptide (melanocortin receptor 1 peptide, MC1R244) as evident from columns in the right part of Fig. 1. These results demonstrate that the peptides with sequence identity 9 and 10 are immunogenic in vivo and upon immunization may elicit an immune response in a warm blooded animal carrying the common human MHC molecule HLA-A2. This finding indicates that the peptides with seq. id. no. 9 and 10 may also be used as a cancer vaccine in humans carrying HLA-A2 and other HLA class I molecules capable of binding these peptides. Furthermore, these results demonstrate that hTERT expressed by the T cell leukemia line Jurkat can be processed by the proteolytic machinery of the cell line to yield peptide fragments identical with or similar to the peptides with sequence identity 9 and 10. Together these observations indicate that an immune response obtained after vaccination of cancer patients or patients at risk of developing cancer with these peptides may result in efficient killing of tumor cells expressing the hTERT subunit of telomerase.

[0075] Fig. 1 depicts cytotoxicity of HLA-A2 transfected Jurkat cells with effector cells obtained from mice immunized as indicated in the figure. Target cells were labeled with ^{51}Cr (0,1 μCi/100 μl cell suspension) for 1 hr. at 37 °C, washed twice and pulsed with peptide (1 μg/ml) for 1 hr at 37 °C before washing. Two thousand labeled, peptide pulsed target cells were seeded per well in a 96 well v-bottom microtitre plate, and effector cells (from $2,5x10^4$ to $2x10^5$) were added to the wells. Cultures were incubated for 4 hrs. at 37 °C and supernatants were harvested and tested in a gamma-counter. The results in Fig. 1 are expressed as specific cytotoxicity calculated by the following formula:

(cpm experimental released - cpm spontaneously released)/

(cpm total - cpm spontaneously released) x 100

Figure 2

[0076] Figure 2 (Fig. 2) shows the results of in vitro stimulation of peripheral blood T cells from a patient (TT) with colon cancer with telomerase (hTERT) derived peptides with sequence identity number 2, 3, 4 and 7. Results in relation to SEQ ID NO: 7 are shown for comparative purposes only. In vitro culture way performed as follows: Triplicates of 10^5 mononuclear cells were incubated for 6 days in X-VIVO 10 medium supplemented with 15% pooled heat inactivated human serum in a humidified incubator in 5% CO_2. Peptides were present throughout culture at a final concentration of 30 μg/ml in the medium. Cultures without peptide served as control. A proliferative response above background values was seen when the T cells were stimulated with the peptide with sequence identity 4. These results demonstrate that blood from a cancer patient contains circulating T cells specific for a peptide derived from telomerase (hTERT). These results demonstrate that the enzymatic subunit of telomerase (hTERT) is immunogenic in man, and may spontaneously give rise to telomerase specific T cell responses when overexpressed by a tumor growing in the patient. Furthermore, one component of the telomerase specific response in this patient is directed against the peptide with seq. id. no. 4 described here. This finding indicates that the peptide with seq. id. no. 4 may also be used as a cancer vaccine in humans. The figure depicts the results of conventional T cell proliferative assays, where peripheral blood mononuclear cells (10^5) were cultured with peptides as indicated for 7 days in triplicates before harvesting. To measure the proliferative capacity of the cultures, ^3H-thymidine ($3,7x10^4$ Bq/ well) was added to the culture overnight before harvesting. Values are given as mean counts per minute (cpm) of the triplicates.

Figures 3 and 4

[0077] Figures 3 and 4 (Fig. 3 and Fig. 4) show the reactivity of tumor infiltrating lymphocytes (TILs) obtained from a patient with advanced pancreatic cancer. The T cells were obtained from a tumor biopsy and was successfully propagated in *vitro* to establish a T cell line. The T cell line was CD3+, CD4+ and CD8-, and proliferated specificially in response to the telomerase peptides. The results in Fig. 3 show T cells that recognise the peptides with seq. id. no. 2 and 3 when compared to controls with medium alone. The results in Fig. 4 show T cells that recognise the peptide with seq. id. no. 2. The TILs were expanded by co-cultureing with recombinant human interleukin 2 (rIL-2) and tested after 14 days in standard proliferation assay using peptides with sequence id. nos. 2, 3, 4 and 7. Results in relation to SEQ ID NO: 7 are shown for comparative purposes only.

Table 1

LMSVYVVEL	FLHWLMSVYVVELLRSFFYVTE
ELLRSFFYV	EARPALLTSRLRFIPK
YVVELLRSF	DGLRPIVNMDYVVGAR
VVELLRSFF	GVPEYGCVVNLRKVVNF
SVYVVELLR	
VELLRSFFY	
YVTETTFQK	
RLFFYRKSV	
SIGIRQHLK	
RPALLTSRL	
ALLTSRLRF	
LLTSRLRFI	
RPIVNMDYV	
LRPIVNMDY	
YVVGARTFR	
VVGARTFRR	
GARTFRREK	
ARTFRREKP	
PPELYFVKV	
ELYFVKVDV	
FVKVDVTGA	
IPQDRLTEV	
DRLTEVIAS	
RLTEVIASI	
IPQGSILSTL	
ILSTLLCSL	
LLRLVDDFL	
RLVDDFLLV	
VPEYGCVVN	
VPEYGCVVNL	
TLVRGVPEY	
FLRTLVRGV	
GVPEYGCVV	
VVNLRKTVV	
GLFPWCGLL	

Table 2

YAETKHFLY
ISDTASLCY
DTDPRRLVQ
AQDPPPELY
LTDLQPYMR
QSDYSSYAR

ILAKFLHWL
ELLRSFFYV
LLARCALFV
WLCHQAFLL
RLVDDFLLV
RLFFYRKSV
LQLPFHQQV
RLGPQGWRL
SLQELTWKM
NVLAFGFAL
VLLKTHCPL
FLLVTPHLT
TLTDLQPYM
RLTEVIASI
FLDLQVNSL
SLNEASSGL
ILSTLLCSL
LLGASVLGL
VLAFGFALL
LQPYMRQFV
LMSVYVVEL
RLPQRYWQM
RQHSSPWQV
YLPNTVTDA
NMRRKLFGV
RLTSRVKAL
LLQAYRFHA
LLDTRTLEV
YMRQFVAHL
LLTSRLRFI
CLVCVPWDA
LLSSLRPSL

Table 2 (Continued)

FMCHHAVRI
LQVNSLQTV
LVAQCLVCV
CLKELVARV
FLRNTKKFI
ALPSDFKTI
VLVHLLARC
VQSDYSSYA
SVWSKLQSI
KLPGTTLTA
QLSRKLPGT
ELYFVKVDV
GLLLDTRTL
WMPGTPRRL
SLTGARRLV
VVIEQSSSL
LPSEAVQWL
QAYRFHACV

GLFDVFLRF
KLFGVLRLK
RLREEILAK
TLVRGVPEY
GLPAPGARR
GLFPWCGLL
KLTRHRVTY
VLPLATFVR
ELVARVLQR

DPRRLVQLL
FVRACLRRL
SVREAGVPL
AGRNMRRKL
LARCALFVL
RPAEEATSL
LPSDFKTIL
LPSEAVQWL
LPGTTLTAL
RPSFLLSSL
LPNTVTDAL
RPALLTSRL

Table 2 (Continued)

RCRAVRSLL
MPRAPRCRA
GIRRDGLLL
VLRLKCHSL
YMRQFVAHL
SLRTAQTQL
QMRPLFLEL
LLRLVDDFL
FVQMPAHGL
HASGPRRRL
VVIEQSSSL
RVISDTASL
CVPAAEHRL
RVKALFSVL
NVLAFGFAL
LVARVLQRL
FAGIRRDGL
HAQCPYGVL
RAQDPPPEL
AYRFHACVL
HAKLSLQEL
GAKGAAGPL
TASLCYSIL
APRCRAVRS
GARRLVETI
AQCPYGVLL
HAKTFLRTL
EATSLEGAL
KAKNAGMSL
AQTQLSRKL
AGIRRDGLL
VLRLKCHSL
ILKAKNAGM
DPRRLVQLL
GAKGAAGPL
FAGIRRDGL
GARRRGGSA
HAKTFLRTL
HAKLSLQEL

Table 2 (Continued)

LARCALFVL
EHRLREEIL
NMRRKLFGV
CAREKPQGS
LTRHRVTYV
RRFLRNTKK
RRDGLLLRL
RREKRAERL
RRLVETIFL
LRFMCHHAV
RRYAVVQKA
KRAERLTSR
RRKLFGVLR
RRRGGSASR
RRLPRLPQR
RRLGPQGWR
LRGSGAWGL
HREARPALL
VRRYAVVQK
ARTSIRASL
HRVTYVPLL
LRSHYREVL
MRPLFLELL
HRAWRTFVL
MRRKLFGVL
LRLVDDFLL
LRRVGDDVL
YRKSVWSKL
QRLCERGAK
FRALVAQCL
SRKLPGTTL
LRRLVPPGL
RRSPGVGCV
RRVGDDVLV
VRGCAWLRR
VRSLLRSHY
ARTFRREKR
SRSLPLPKR
IRASLTFNR

Table 2 (Continued)

LREEILAKF
IRRDGLLLR
QRGDPAAFR
LRPIVNMDY
ARRLVETIF
ARPALLTSR
LRPSLTGAR
LRLKCHSLF
FRREKRAER
ARGGPPEAF
CRAVRSLLR
GRTRGPSDR
RRRLGCERA
LRELSEAEV
ARCALFVLV
RPAEEATSL
DPRRLVQLL
RPSFLLSSL
LPSEAVQWL
RPALLTSRL
LPSDFKTIL
RPPPAAPSF
LPRLPQRYW
LPNTVTDAL
LPGTTLTAL
LAKFLHWLM
KAKNAGMSL
GSRHNERRF
KALFSVLNY
SPLRDAVVI
RAQDPPPEL
MPAHGLFPW
AEVRQHREA
REAGVPLGL
EEATSLEGA
LEAAANPAL
QETSPLRDA
REVLPLATF

Table 2 (Continued)

KEQLRPSFL
REKPQGSVA
LEVQSDYSS
REARPALLT
EEDTDPRRL
REEILAKFL
CERGAKNVL
DDVLVHLLA
GDMENKLFA
YERARRPGL

Sequence Identity List

SEQUENCE LISTING

COMMON FOR ALL SEQUENCES.

SEQUENCE TYPE: Peptide

SEQUENCE UNIT: Amino Acid

TOPOLOGY: Linear

SEQUENCE ID NO: 1

[0078] SEQUENCE LENGTH: 22 amino acids

F	L	H	W	L	M	S	V	Y	V	V	E	L	L	R	S	F	F	Y	V	T	E
1					5					10					15					20	

SEQUENCE ID NO: 2

[0079] SEQUENCE LENGTH: 16 amino acids

E	A	R	P	A	L	L	T	S	R	L	R	F	I	P	K
1				5				10				15			

SEQUENCE ID NO: 3

[0080] SEQUENCE LENGTH: 16 amino acids

D G L R P I V N M D Y V V G A R

1 5 10 15

SEQUENCE ID NO: 4

[0081] SEQUENCE LENGTH: 18 amino acids

G V P E Y G C V V N L R K T V V N F

1 5 10 15

SEQUENCE ID NO: 5

[0082] SEQUENCE LENGTH: 23 amino acids

K F L H W L M S V Y V V E L L R S F F Y V T E

1 5 10 15 20

SEQUENCE ID NO: 6

[0083] SEQUENCE LENGTH: 17 amino acids

K F L H W L M S V Y V V E L L R S

1 5 10 15

SEQUENCE ID NO: 7

[0084] SEQUENCE LENGTH: 18 amino acids

L M S V Y V V E L L R S F F Y V T E

1 5 10 15

SEQUENCE ID NO: 9

[0085] SEQUENCE LENGTH: 9 amino acids

I L A K F L H W L

1 5

SEQUENCE ID NO: 10

[0086] SEQUENCE LENGTH: 9 amino acids

E L L R S F F Y V

1 5

SEQUENCE ID NO: 11

[0087] SEQUENCE LENGTH: 9 amino acids

L M S V Y V V E L

1 5

SEQUENCE ID NO: 12

[0088] SEQUENCE LENGTH: 9 amino acids

T S R L R F I P K

1 5

SEQUENCE ID NO: 13

[0089] SEQUENCE LENGTH: 9 amino acids

L T S R L R F I P

1 5

SEQUENCE ID NO: 14

[0090] SEQUENCE LENGTH: 9 amino acids

L L T S R L R F I

1 5

SEQUENCE ID NO: 15

[0091] SEQUENCE LENGTH: 9 amino acids

A L L T S R L R F

1 5

SEQUENCE ID NO: 16

[0092] SEQUENCE LENGTH: 9 amino acids

P A L L T S R L R

1 5

SEQUENCE ID NO: 17

[0093] SEQUENCE LENGTH: 9 amino acids

R P A L L T S R L

1 5

SEQUENCE ID NO: 18

[0094] SEQUENCE LENGTH: 9 amino acids

A R P A L L T S R

1 5

SEQUENCE ID NO: 19

[0095] SEQUENCE LENGTH: 9 amino acids

E A R P A L L T S

1 5

Claims

1. The use of a peptide for the manufacture of a medicament for the treatment or prophylaxis of cancer, the peptide comprising a sequence EARPALLTSRLRFIPK (SEQ ID NO: 2), DGLRPIVNMDYVVGAR (SEQ ID NO: 3), GVPEYGCVVNLRKTVVNF (SEQ ID NO: 4), ILAKFLHWL (SEQ ID NO: 9) or ELLRSFFYV (SEQ ID NO: 10), the treatment or prophylaxis comprising generating a T cell response, the response being against the peptide EARPALLTSRLRFIPK (SEQ ID NO: 2), DGLRPIVNMDYVVGAR (SEQ ID NO: 3), GVPEYGCVVNLRKTVVNF (SEQ ID NO: 4), ILAKFLHWL (SEQ ID NO: 9) or ELLRSFFYV (SEQ ID NO: 10) or a fragment thereof, at least 8 amino acids long, producible after processing by an antigen presenting cell.

2. The use of a nucleic acid for the manufacture of a medicament for the treatment or prophylaxis of cancer, in which the nucleic acid is capable of encoding a peptide comprising a sequence EARPALLTSRLRFIPK (SEQ ID NO: 2), DGLRPIVNMDYVVGAR (SEQ ID NO: 3), GVPEYGCVVNLRKTVVNF (SEQ ID NO: 4), ILAKFLHWL (SEQ ID NO: 9) or ELLRSFFYV (SEQ ID NO: 10), the treatment or prophylaxis comprising generating a T cell response, the response being against the peptide EARPALLTSRLRFIPK (SEQ ID NO: 2), DGLRPIVNMDYVVGAR (SEQ ID NO: 3), GVPEYGCWNLRKTWNF (SEQ ID NO: 4), ILAKFLHWL (SEQ ID NO: 9) or ELLRSFFYV (SEQ ID NO: 10) or a fragment thereof, at least 8 amino acids long, producible after processing by an antigen presenting cell.

3. Use according to Claim 1 or 2, in which the treatment or prophylaxis comprises administering to a mammal suffering or likely to suffer from cancer a therapeutically or prophylactically effective amount of the peptide so that a T cell response directed against the telomerase is induced in the mammal.

4. Use according to any one of Claims 1 to 3 in which the T cell response induced is a cytotoxic T cell response.

5. Use according to any one of Claims 1 to 4 wherein the medicament is a pharmaceutical composition comprising

the peptide or nucleic acid, together with a pharmaceutically acceptable carrier or diluent.

6. Use according to any one of Claims 1 or 3 to 5 wherein the treatment or prophylaxis comprises mixing at least one peptide comprising the sequence EARPALLTSRLRFIPK (SEQ ID NO: 2), DGLRPIVNMDYVVGAR (SEQ ID NO: 3), GVPEYGCWNLRKTVVNF (SEQ ID NO: 4), ILAKFLHWL (SEQ ID NO: 9) or ELLRSFFYV (SEQ ID NO: 10) with a pharmaceutically acceptable carrier or diluent.

7. Use according to any of Claims 2 to 5 wherein the treatment or prophylaxis comprises mixing at least one nucleic acid that is capable of encoding a peptide comprising the sequence EARPALLTSRLRFIPK (SEQ ID NO: 2), DGLRPIVNMDYVVGAR (SEQ ID NO: 3), GVPEYGCVVNLRKTVVNF (SEQ ID NO: 4), ILAKFLHWL (SEQ ID NO: 9) or ELLRSFFYV (SEQ ID NO: 10) with a pharmaceutically acceptable carrier or diluent.

8. Use according to any one of Claims 1 or 2 to 7 wherein the medicament comprises the peptide comprising the sequence EARPALLTSRLRFIPK (SEQ ID NO: 2), DGLRPIVNMDYWGAR (SEQ ID NO: 3), GVPEYGCVVNLRKTVVNF (SEQ ID NO: 4), ILAKFLHWL (SEQ ID NO: 9) or ELLRSFFYV (SEQ ID NO: 10) and at least one peptide capable of inducing a T cell response directed against an oncogene or mutant tumour suppressor protein or peptide, together with a pharmaceutically acceptable carrier or diluent.

9. Use according to Claim 8 wherein the treatment or prophylaxis comprises mixing the peptide comprising the sequence EARPALLTSRLRFIPK (SEQ ID NO: 2), DGLRPIVNMDYVVGAR (SEQ ID NO: 3), GVPEYGCVVNLRKTVVNF (SEQ ID NO: 4), ILAKFLHWL (SEQ ID NO: 9) or ELLRSFFYV (SEQ ID NO: 10) with at least one peptide capable of inducing a T cell response directed against an oncogene or mutant tumour suppressor protein or peptide, and a pharmaceutically acceptable carrier or diluent.

10. Use according to Claim 8 or 9 in which the oncogene protein or peptide is a mutant p21-ras protein or peptide, or in which the tumour suppressor protein or peptide is a retinoblastoma or p53 protein or peptide.

11. Use according to any one of the preceding claims, in which the cancer is selected from breast cancer, prostate cancer, pancreatic cancer, colorectal cancer, lung cancer, malignant melanoma, leukaemias, lymphomas, ovarian cancer, cervical cancer and biliary tract carcinomas.

12. A method of generating T lymphocytes capable of recognising and destroying tumour cells in a mammal, in which the method comprises culturing a sample of T lymphocytes taken from a mammal in the presence of a peptide in an amount sufficient to generate telomerase specific T lymphocytes, in which the peptide comprises a sequence EARPALLTSRLRFIPK (SEQ ID NO: 2), DGLRPIVNMDYVVGAR (SEQ ID NO: 3), GVPEYGCVVNLRKTVVNF (SEQ ID NO: 4), ILAKFLHWL (SEQ ID NO: 9) or ELLRSFFYV (SEQ ID NO: 10), wherein the telomerase specific T lymphocytes generate a response against the peptide EARPALLTSRLRFIPK (SEQ ID NO: 2), DGLRPIVNMDYVVGAR (SEQ ID NO: 3), GVPEYGCWNLRKTVVNF (SEQ ID NO: 4), ILAKFLHWL (SEQ ID NO: 9) or ELLRSFFYV (SEQ ID NO: 10) or a fragment thereof, at least 8 amino acids long, producible after processing by an antigen presenting cell.

13. A telomerase specific T lymphocyte generated by a method according to Claim 12.

14. A pharmaceutical composition comprising a telomerase specific T lymphocyte according to Claim 13, together with a pharmaceutically acceptable carrier.

15. The use of a combination of a telomerase peptide and a peptide capable of inducing a T cell response against an oncogene or mutant tumour suppressor protein or peptide for the manufacture of a medicament for the treatment or prophylaxis of cancer, the telomerase peptide comprising a sequence EARPALLTSRLRFIPK (SEQ ID NO: 2), DGLRPIVNMDYVVGAR (SEQ ID NO: 3), GVPEYGCVVNLRKTVVNF (SEQ ID NO: 4), ILAKFLHWL (SEQ ID NO: 9) or ELLRSFFYV (SEQ ID NO: 10) and the treatment or prophylaxis comprises generating a T cell response, the response being against the peptide EARPALLTSRLRFIPK (SEQ ID NO: 2), DGLRPIVNMDYVVGAR (SEQ ID NO: 3), GVPEYGCVVNLRKTVVNF (SEQ ID NO: 4), ILAKFLHVVL (SEQ ID NO: 9) or ELLRSFFYV (SEQ ID NO: 10) or a fragment thereof, at least 8 amino acids long, producible after processing by an antigen presenting cell.

16. Use according to any one of Claims 1 to 11, the method of Claim 12, the T lymphocyte of Claim 13 or the pharmaceutical of Claim 14 wherein the peptide comprising the sequence EARPALLTSRLRFIPK (SEQ ID NO: 2), DGLRPIVNMDYVVGAR (SEQ ID NO: 3), GVPEYGCVVNLRKTVVNF (SEQ ID NO: 4), ILAKFLHWL (SEQ ID NO:

9) or ELLRSFFYV (SEQ ID NO: 10) contains between 9 and 25 amino acids.

Patentansprüche

1. Verwendung eines Peptids zur Herstellung eines Medikaments zur Behandlung oder Prophylaxe von Krebs, wobei das Peptid eine Sequenz EARPALLTSRLRFIPK (SEQ ID NR. 2), DGLRPIVNMDYVVGAR (SEQ ID NR. 3), GVPEYGCVVNLRKTVVNF (SEQ ID NR. 4), ILAKFLHWL (SEQ ID NR. 9) oder ELLRSFFYV (SEQ ID NR. 10) umfasst, wobei die Behandlung oder Prophylaxe die Erzeugung einer T-Zell-Antwort umfasst, wobei die Antwort gegen das Peplid EARPALLTSRLRFIPK (SEQ ID NR. 2), DGLRPIVNMDYVVGAR (SEQ ID NR. 3), GVPEYGCVVNLRKTVVNF (SEQ ID NR. 4), ILAKFLHWL (SEQ ID NR. 9) oder ELLRSFFYV (SEQ ID NR. 10) oder ein Fragment davon gerichtet ist, das wenigstens 8 Aminosäuren lang ist, das nach Verarbeitung durch eine Artigen-präsentierende Zelle produzierbar ist.

2. Verwendung einer Nucleinsäure zur Herstellung eines Medikaments zur Behandlung oder Prophylaxe von Krebs, wobei die Nucleinsäure in der Lage ist, ein Peptid zu kodieren, das eine Sequenz EARPALLTSRLRFIPK (SEQ ID NR. 2), DGLRPIVNMDYVVGAR (SEQ ID NR. 3), GVPEYGCVVNLRKTVVNF (SEQ ID NR. 4), ILAKFLHWL (SEQ ID NR. 9) oder ELLRSFFYV (SEQ ID NR. 10) umfasst, wobei die Behandlung oder Prophylaxe die Erzeugung einer T-Zell-Antwort umfasst, wobei die Antwort gegen das Peptid EARPALLTSRLRFIPK (SEQ ID NR. 2), DGLRPIVNMDYVVGAR (SEQ ID NR. 3), GVPEYGCVVNLRKTVVNF (SEQ ID NR. 4), ILAKFLHWL (SEQ ID NR. 9) oder ELLRSFFYV (SEQ ID NR. 10) oder ein Fragment davon gerichtet ist, das wenigstens 8 Aminosäuren lang ist, das nach Verarbeitung durch eine Antigen-präsentierende Zelle produzierbar ist.

3. Verwendung nach Anspruch 1 oder 2, wobei die Behandlung oder Prophylaxe die Verabreichung einer therapeutisch oder prophylaktisch wirksamen Menge des Peptids an ein Säugetier umfasst, das an Krebs leidet oder wahrscheinlich leidet, so dass eine T-Zell-Antwort, die gegen die Telomerase gerichtet ist, im Säugetier induziert wird.

4. Verwendung nach einem der Ansprüche 1 bis 3, wobei die induzierte T-Zell-Antwort eine zytotoxische T-Zell-Antwort ist.

5. Verwendung nach einem der Ansprüche 1 bis 4, wobei das Medikament ein Arzneimittel, umfassend das Peptid oder die Nucleinsäure, zusammen mit einem pharmazeutisch verträglichen Träger oder Verdünnungsmittel ist.

6. Verwendung nach einem der Ansprüche 1 oder 3 bis 5, wobei die Behandlung oder Prophylaxe das Mischen wenigstens eines Peptids, das die Sequenz EARPALLTSRLRFIPK (SEQ ID NR. 2), DGLRPIVNMDYVVGAR (SEQ ID NR. 3), GVPEYGCVVNLRKTVVNF (SEQ ID NR. 4), ILAKFLHWL (SEQ ID NR. 9) oder ELLRSFFYV (SEQ ID NR. 10) umfasst, mit einem pharmazeutisch verträglichen Träger oder Verdünnungsmittel umfasst.

7. Verwendung nach einem der Ansprüche 2 bis 5, wobei die Behandlung oder Prophylaxe das Mischen wenigstens einer Nucleinsäure, die in der Lage ist, ein Peptid zu kodieren, das die Sequenz EARPALLTSRLRFIPK (SEQ ID NR. 2), DGLRPIVNMDYVVGAR (SEQ ID NR. 3), GVPEYGCVVNLRKTVVNF (SEQ ID NR. 4), ILAKFLHWL (SEQ ID NR. 9) oder ELLRSFFYV (SEQ ID NR. 10) umfasst, mit einem pharmazeutisch verträglichen Träger oder Verdünnungsmittel umfasst.

8. Verwendung nach einem der Ansprüche 1 oder 2 bis 7, wobei das Medikament das Peptid, das die Sequenz EARPALLTSRLRFIPK (SEQ ID NR. 2), DGLRPIVNMDYVVGAR (SEQ ID NR. 3), GVPEYGCVVNLRKTVVNF (SEQ ID NR. 4), ILAKFLHWL (SEQ ID NR. 9) oder ELLRSFFYV (SEQ ID NR. 10) umfasst, und wenigstens ein Peptid, das in der Lage ist, eine T-Zell-Antwort, die gegen ein Onkogen- oder eine Mutante eines Tumorsuppressorproteins oder -peptids gerichtet ist, zu induzieren, zusammen mit einem pharmazeutisch verträglichen Träger oder Verdünnungsmittel umfasst.

9. Verwendung nach Anspruch 8, wobei die Behandlung oder Prophylaxe das Mischen des Peptids, das die Sequenz EARPALLTSRLRFIPK (SEQ ID NR. 2), DGLRPIVNMDYVVGAR (SEQ ID NR. 3), GVPEYGCVVNLRKTVVNF (SEQ ID NR. 4), ILAKFLHWL (SEQ ID NR. 9) oder ELLRSFFYV (SEQ ID NR. 10) umfasst, mit wenigstens einem Peptid, das in der Lage ist, eine T-Zell-Antwort, die gegen ein Onkogen- oder eine Mutante eines Tumorsuppressorproteins oder -peptids gerichtet ist, zu induzieren, und einen pharmazeutisch verträglichen Träger oder Verdünnungsmittel umfasst.

10. Verwendung nach Anspruch 8 oder 9, wobei das Onkogenprotein oder -peptid eine Mutante des p21-res-Proteins oder -peptids ist, oder wobei das Tumorsuppressorprotein oder -peptid ein Retinoblastom- oder p53-Protein oder -peptid ist.

11. Verwendung nach einem der vorangegangenen Ansprüche, wobei der Krebs ausgewählt ist aus Brustkrebs, Prostatakrebs, Pankreaskrebs, kolonektalem Krebs, Lungenkrebs, malignem Melanom, Leukämie, Lymphomen, Ovarialkrebs, Zarvixkrebs und Gallentraktkarzinomen.

12. Verfahren zur Erzeugung von T-Lymphozyten, die in der Lage sind, Tumorzellen in einem Säugetier zu erkennen und zu zerstören, wobei das Verfahren das Kultivieren einer Probe von T-Lymphozyten, die aus einem Säugetier entnommen wurden, in Gegenwart eines Peptids in einer Menge, die ausreichend ist, Telomerase-spezifische T-Lymphozyten zu erzeugen, wobei das Peptid eine Sequenz EARPALLTSRLRFIPK (SEQ ID NR. 2), DGLRPIVNMDYVVGAR (SEQ ID NR. 3), GVPEYGCVVNLRKTVVNF (SEQ ID NR. 4), ILAKFLHWL (SEQ ID NR. 9) oder ELLRSFFYV (SEQ ID NR. 10) umfasst, wobei die Telomerase-spezifischen T-Lymphozyten eine Antwort gegen das Peptid EARPALLTSRLRFIPK (SEQ ID NR. 2), DGLRPIVNMDYVVGAR (SEQ ID NR. 3), GVPEYGCVVNLRKTVVNF (SEQ ID NR. 4), ILAKFLHWL (SEQ ID NR. 9) oder ELLRSFFYV (SEQ ID NR. 10) oder ein Fragment davon erzeugen, das wenigstens 8 Aminosäuren lang ist, das nach Verarbeitung durch eine Antigen-präsentierende Zelle produzierbar ist.

13. Telomerase-spezifischer T-Lymphozyt, der mit einem Verfahren nach Anspruch 12 erzeugt wird.

14. Arzneimittel, umfassend einen Telomerase-spezifischen T-Lymphozyten nach Anspruch 13, zusammen mit einem pharmazeutisch verträglichen Träger.

15. Verwendung einer Kombination eines Telomerase-Peptids und eines Peptids, das in der Lage ist, eine T-Zell-Antwort gegen ein Onkogen- oder eine Mutante eines Tumorsuppressorproteins oder -peptids zu induzieren, zur Herstellung eines Medikaments zur Behandlung oder Prophylaxe von Krebs, wobei das Telomerase-Peptid eine Sequenz EARPALLTSRLRFIPK (SEQ ID NR. 2), DGLRPIVNMDYVVGAR (SEQ ID NR. 3), GVPEYGCVVNLRKTVVNF (SEQ ID NR. 4), ILAKFLHWL (SEQ ID NR. 9) oder ELLRSFFYV (SEQ ID NR. 10) umfasst, und die Behandlung oder Prophylaxe umfasst die Erzeugung einer T-Zell-Antwort, wobei sich die Antwort gegen das Peptld EARPALLTSRLRFIPK (SEQ ID NR. 2), DGLRPIVNMDYVVGAR (SEQ ID NR. 3), GVPEYGCVVNLRKTVVNF (SEQ ID NR. 4), ILAKFLHWL (SEQ ID NR. 9) oder ELLRSFFYV (SEQ ID NR. 10) oder ein Fragment davon richtet, das wenigstens 8 Aminosäuren lang ist, das nach Verarbeitung durch eine Artigen-präsentierende Zelle produzierbar ist

16. Verwendung nach einem der Ansprüche 1 bis 11, Verfahren nach Anspruch 12, T-Lymphozyt nach Anspruch 13 oder Arzneimittel nach Anspruch 14, wobei das Peptid, das die Sequenz EARPALLTSRLRFIPK (SEQ ID NR. 2), DGLRPIVNMDYVVGAR (SEQ ID NR. 3), GVPEYGCVVNLRKTVVNF (SEQ ID NR. 4), ILAKFLHWL (SEQ ID NR. 9) oder ELLRSFFYV (SEQ ID NR. 10) umfasst, zwischen 9 und 25 Aminosäuren enthält.

Revendications

1. Utilisation d'un peptide pour la fabrication d'un médicament destiné au traitement ou à la prophylaxie du cancer, le peptide comprenant une séquence EARPALLTSRLRFIPK (SEQ ID NO : 2), DGLRPIVNMDYVVGAR (SEQ ID NO : 3), GVPEYGCVVNLRKTVVNF (SEQ ID NO : 4), ILAKFLHVVL (SEQ ID NO :9) ou BLLRSFFYV (SEQ ID NO: 10), le traitement ou la prophylaxie comprenant la production d'une réponse cellulaire de type T, la réponse étant dirigée contre le peptide EARPALLTSRLRFIPK (SEQ ID NO: 2), DGLRPIVNMDYVVGAR (SEQ ID NO: 3), GVPEYGCVVNLRKTVVNF (SEQ ID NO: 4), ILAKFLHVVL (SEQ ID NO:9) ou ELLRSFFYV (SEQ ID NO: 10) ou un fragment de l'un de ces derniers, long d'au moins B acides aminés, qui peut être produit après traitement par une cellule présentatrice d'antigènes.

2. Utilisation d'un acide nucléique pour la fabrication d'un médicament destiné au traitement ou à la prophylaxie du cancer, dans laquelle l'acide nucléique est capable de coder un peptide comprenant une séquence EARPALLTSRLRFIPK (SEQ ID NO: 2), DGLRPIVNMDYVVGAR (SEQ ID NO: 3), GVPEYGCVVNLRKTVVNF (SEQ ID NO: 4), ILAKFLHVVL (SEQ ID NO:9) ou ELLRSFFYV (SEQ ID NO: 10), le traitement ou la prophylaxie comprenant la production d'une réponse cellulaire de type T, la réponse étant dirigée contre le peptide EARPALLTSRLRFIPK (SEQ ID NO: 2), DGLRPIVNMDYVVGAR (SEQ ID NO: 3), GVPEYGCVVNLRKTVVNF (SEQ ID NO: 4), ILAKFL-

HVVL (SEQ ID NO:9) ou ELLRSFFYV (SEQ ID NO: 10) ou un fragment de ces derniers, long d'au moins 8 acides aminés, qui peut être produit après traitement par une cellule présentatrice d'antigènes.

3. Utilisation selon la revendication 1 ou 2, dans laquelle le traitement ou la prophylaxie comprend l'administration à un mammifère souffrant ou susceptible de souffrir du cancer d'une quantité du peptide efficace d'un point de vue thérapeutique ou prophylactique de telle sorte qu'une réponse cellulaire de type T dirigée contre la télomérase est induite chez le mammifère.

4. Utilisation selon l'une quelconque des revendications 1 à 3, dans laquelle la réponse cellulaire de type T induite est une réponse cellulaire de type T cytotoxique.

5. Utilisation selon l'une quelconque des revendications 1 à 4, dans laquelle le médicament est une composition pharmaceutique comprenant le peptide ou l'acide nucléique, associé à un véhicule ou à un diluant acceptables d'un point de vue pharmaceutique.

6. Utilisation selon l'une quelconque des revendications 1 ou 3 à 5, dans laquelle le traitement ou la prophylaxie comprend le mélange d'au moins un peptide comprenant la séquence EARPALLTSRLRFIPK (SEQ ID NO: 2), DGLRPIVNMDYVVGAR (SEQ ID NO: 3), GVPEYGCVVNLRKTVVNF (SEQ ID NO: 4), ILAKFLHVVL (SEQ ID NO: 9) ou ELLRSFFYV (SEQ ID NO: 10) avec un véhicule ou un diluant acceptables d'un point de vue pharmaceutique.

7. Utilisation selon l'une quelconque des revendications 2 à 5, dans laquelle le traitement ou la prophylaxie comprend le mélange d'au moins un acide nucléique qui est apte à coder un peptide comprenant la séquence EARPALLTSRLRFIPK (SEQ ID NO: 2), DGLRPIVNMDYVVGAR (SEQ ID NO: 3), GVPEYGCVVNLRKTVVNF (SEQ ID NO: 4), ILAKFLHVVL (SEQ ID NO:9) ou ELLRSFFYV (SEQ ID NO: 10) avec un véhicule ou un diluant acceptables d'un point de vue pharmaceutique.

8. Utilisation selon l'une quelconque des revendications 1 ou 2 à 7, dans laquelle le médicament comprend le peptide comprenant la séquence EARPALLTSRLRFIPK (SEQ ID NO: 2), DGLRPIVNMDYVVGAR (SEQ ID NO: 3), GVPEYGCVVNLRKTVVNF (SEQ ID NO: 4), ILAKFLHVVL (SEQ ID NO:9) ou ELLRSFFYV (SEQ ID NO: 10) et au moins un peptide apte à induire une réponse cellulaire de type T dirigée contre une protéine ou un peptide oncogènes ou une protéine ou un peptide suppresseurs de tumeur mutants, associés à un véhicule ou à un diluant acceptables d'un point de vue pharmaceutique.

9. Utilisation selon la revendication 8, dans laquelle le traitement ou la prophylaxie comprend le mélange d'un peptide comprenant la séquence EARPALLTSRLRFIPK (SEQ ID NO: 2), DGLRPIVNMDYVVGAR (SEQ ID NO: 3), GVPEYGCVVNLRKTVVNF (SEQ ID NO: 4), ILAKFLHVVL (SEQ ID NO:9) ou ELLRSFFYV (SEQ ID NO: 10) avec au moins un peptide apte à induire une réponse cellulaire de type T dirigée contre une protéine ou un peptide oncogènes ou une protéine ou un peptide suppresseurs de tumeur mutants, et avec un véhicule ou un diluant acceptables d'un point de vue pharmaceutique.

10. Utilisation selon la revendication 8 ou 9, dans laquelle la protéine ou le peptide oncogènes est une protéine ou un peptide mutants p21-ras, ou dans laquelle la protéine ou le peptide suppresseurs de tumeur est un retinoblastome ou une protéine ou un peptide p53.

11. Utilisation selon l'une quelconque des revendications précédentes, dans laquelle le cancer est choisi dans le groupe constitué par le cancer du sein, le cancer de la prostate, le cancer du pancréas, le cancer colorectal, le cancer du poumon, le mélanome malin, les leucémies, les lymphomes, le cancer de l'ovaire, le cancer cervical et les carcinomes des voles biliaires.

12. Procédé de production de lymphocytes T aptes à reconnaître et à détruire des cellules tumorales chez un mammifère, dans lequel le procédé comprend la culture d'un échantillon de lymphocytes T prélevé chez un mammifère en présence d'un peptide en une quantité suffisante pour produire des lymphocytes T spécifiques de la télomérase, ledit peptide comprenant une séquence EARPALLTSRLRFIPK (SEQ ID NO: 2), DGLRPIVNMDYVVGAR (SEQ ID NO: 3), GVPEYGCVVNLRKTVVNF (SEQ ID NO: 4), ILAKFLHVVL (SEQ ID NO:9) ou ELLRSFFYV (SEQ ID NO: 10), lesdits lymphocytes T spécifiques de la télomérase produisant une réponse dirigée contre le peptide EARPALLTSRLRFIPK (SEQ ID NO: 2), DGLRPIVNMDYVVGAR (SEQ ID NO: 3), GVPEYGCVVNLRKTVVNF (SEQ ID NO: 4), ILAKFLHVVL (SEQ ID NO:9) ou ELLRSFFYV (SEQ ID NO: 10) ou un fragment de ces derniers, long d'au moins 8 acides aminés, qui peut être produit après traitement par une cellule présentatrice d'antigènes.

13. Lymphocyte T spécifique de la télomérase obtenu par un procédé selon la revendication 12.

14. Composition pharmaceutique comprenant un lymphocyte T spécifique de la télomérase selon la revendication 13 associé à un véhicule acceptable d'un point de vue pharmaceutique.

15. Utilisation de l'association d'un peptide de télomérase et d'un peptide apte à induire une réponse cellulaire de type T dirigée contre une protéine ou un peptide oncogènes ou une protéine ou un peptide suppresseurs de tumeur mutants en vue de la fabrication d'un médicament destiné au traitement ou à la prophylaxie du cancer, le peptide de télomérase comprenant une séquence EARPALLTSRLRFIPK (SEQ ID NO: 2), DGLRPIVNMDYVVGAR (SEQ ID NO: 3), GVPEYGCVVNLRKTVVNF (SEQ ID NO: 4), ILAKFLHVVL (SEQ ID NO:9) ou ELLRSFFYV (SEQ ID NO: 10), utilisation dans laquelle le traitement ou la prophylaxie comprend la production d'une réponse cellulaire de type T, la réponse étant dirigée contre le peptide EARPALLTSRLRFIPK (SEQ ID NO: 2), DGLRPIVN-MDYVVGAR (SEQ ID NO: 3), GVPEYGCVVNLRKTVVNF (SEQ ID NO: 4), ILAKFLHVVL (SEQ ID NO:9) ou EL-LRSFFYV (SEQ ID NO: 10), ou un fragment de ces derniers, long d'au moins 8 acides aminés, qui peut être produit après traitement par une cellule présentatrice d'antigènes.

16. Utilisation selon l'une quelconque des revendications 1 à 11, procédé selon la revendication 12, lymphocyte T selon la revendication 13 ou composition pharmaceutique selon la revendication 14, **caractérisés en ce que** le peptide comprenant une séquence EARPALLTSRLRFIPK (SEQ ID NO: 2), DGLRPIVNMDYVVGAR (SEQ ID NO: 3), GVPEYGCVVNLRKTVVNF (SEQ ID NO: 4), ILAKFLHVVL (SEQ ID NO:9) ou ELLRSFFYV (SEQ ID NO: 10) contient de 9 à 25 acides aminés.

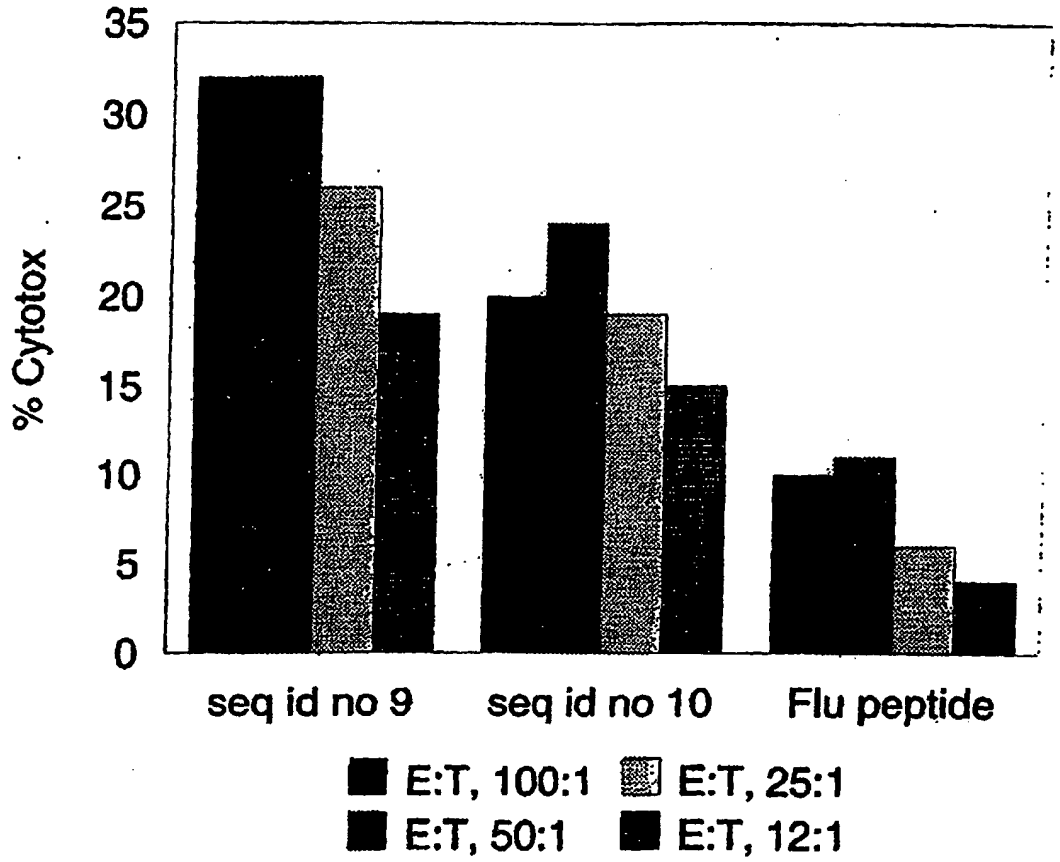

Fig. 1

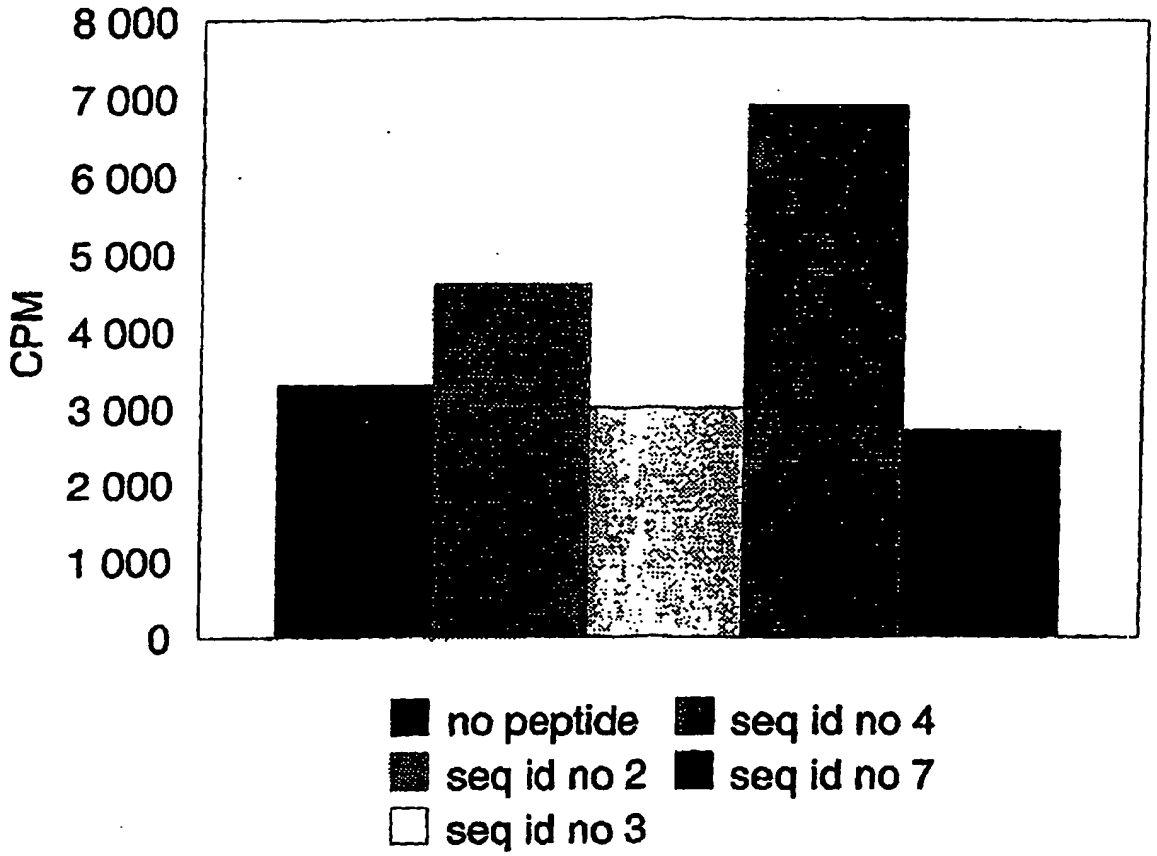

Fig. 2

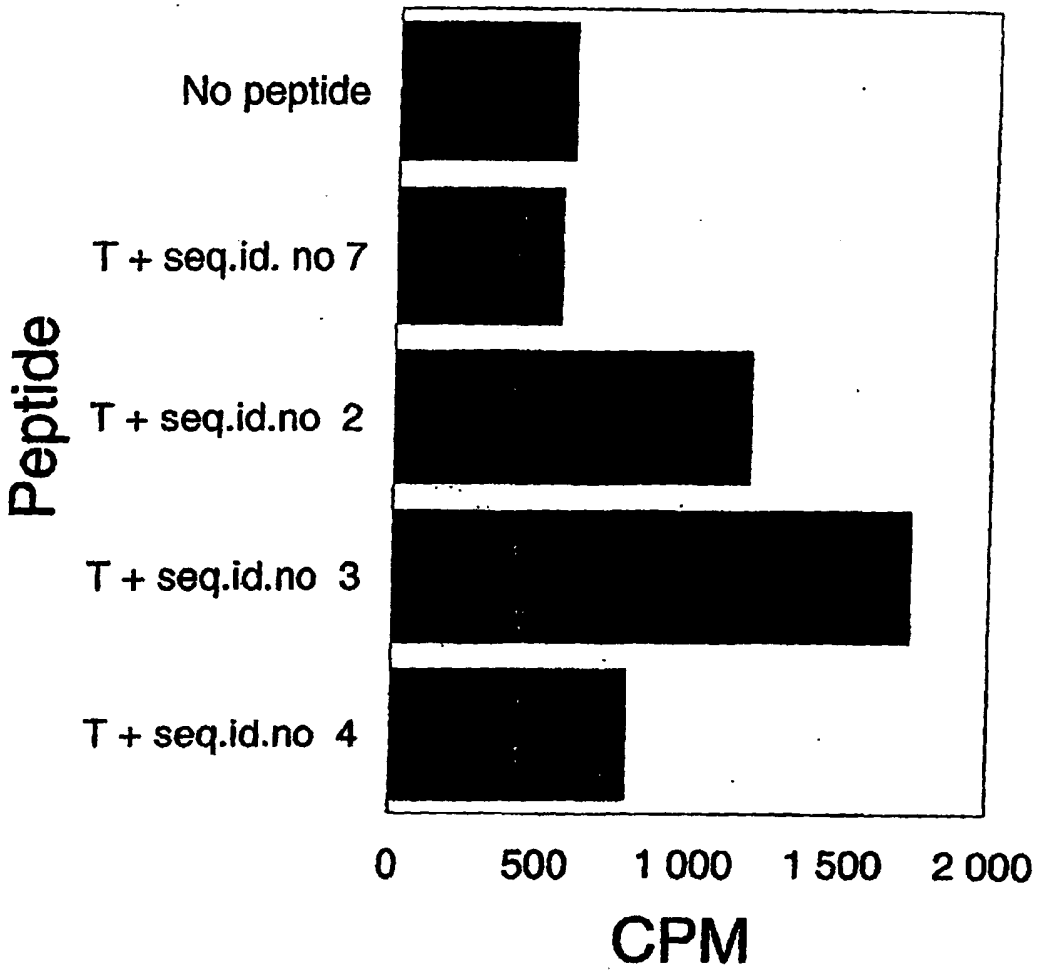

Fig. 3

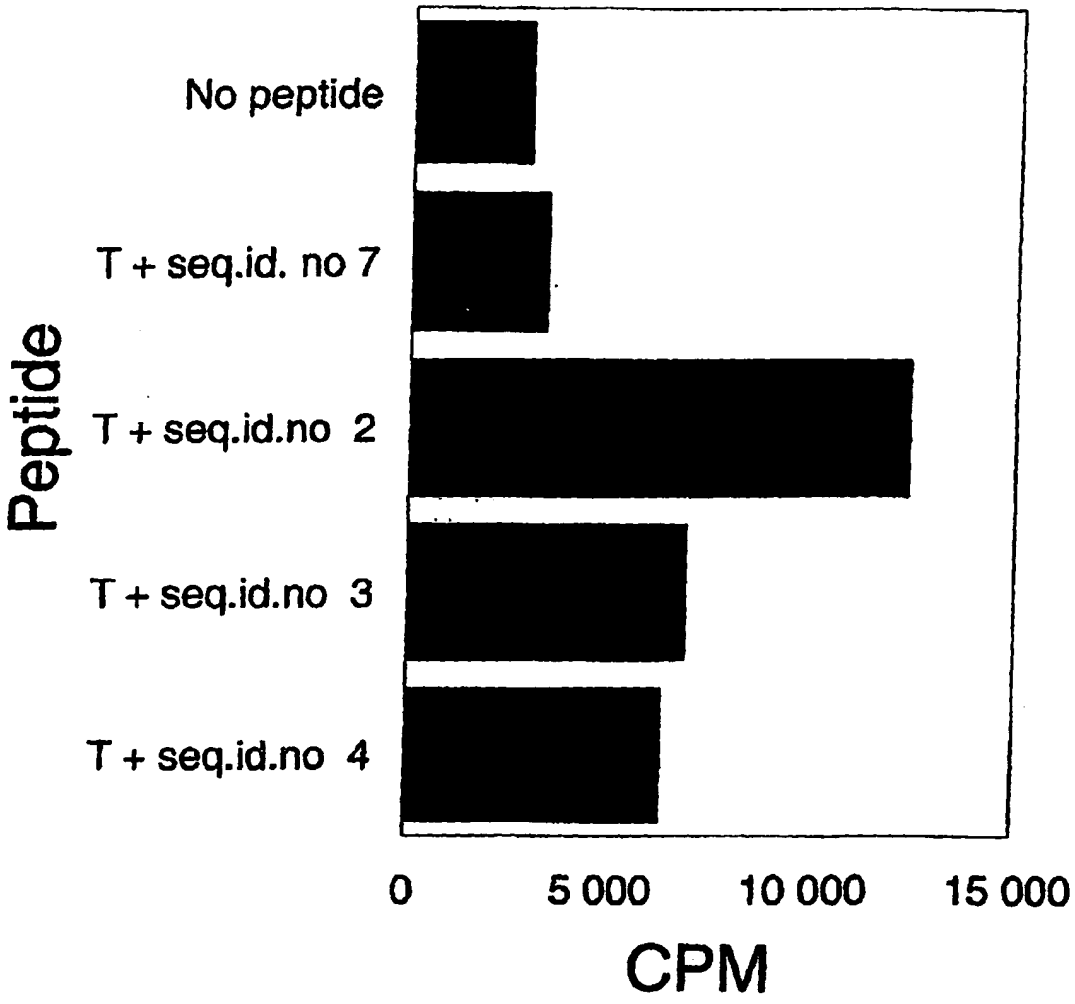

Fig. 4